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ORTHOSTATIC TOLERANCE DURING α_1-ADRENERGIC RECEPTOR BLOCKADE AT HIGH ALTITUDE

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In the first two weeks of high altitude (HA) exposure, blood pressure typically rises due, in part, to a large increase in sympathetic stimulation. We hypothesized that blocking a1-adrenergic receptors would impair circulatory compensation to an orthostatic challenge to a greater extent at HA than at sea level (SL). Sixteen healthy women (23 ± 2 yr) were randomly assigned to receive either 2 mg prazosin (n=8) or placebo (n=8) t.i.d. (double-blind design) for 12 d at SL and during the first 12 d of HA residence (4300 m). Passive 60° upright tilt was performed at SL (10 d of treatment), and after 3 and 10 d at HA. Mean arterial blood pressure (MBP, auscultation) and heart rate (HR, ECG) were measured every min during 10 min each of supine rest and tilt. For the prazosin group compared to the placebo group: 1. At SL, supine and tilt MBP were lower ($P<0.05$) and, at HA, MBP was lower only in the first several min of tilt on day 10 ($P<0.05$); 2. At SL or HA, HR was similar for either position; and 3. From supine to tilt, the drop in MBP was greater only at SL and the increase in HR was consistently greater only at HA (both $P<0.05$). We conclude that a1-adrenergic blockade altered MBP and HR responses to tilt at SL and HA, but that orthostatic tolerance was well maintained in both environments. Compensatory adjustments were likely in either sympathetic and parasympathetic neural discharge or in other receptor activities.

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BACKGROUND

The current study was performed during the third year of a three-year collaborative project within the Defense Women's Health Research Program (DWHRP). The name of the project was titled "*Women at Altitude: Effects of Menstrual Cycle Phase and Alpha-Adrenergic Blockade on High-Altitude Acclimatization*". Involved were investigators from USARIEM, the Palo Alto Veteran's Affairs Health Care System, Palo Alto, CA, and the University of Colorado Health Sciences Center, Denver, CO.

The major purpose of the third year was to study the α-adrenergic contribution to altitude acclimatization in women during the first 12 days of residence at 4300 m. The approach used was to block some of the α-adrenergic receptors using prazosin (a selective α_1-adrenergic receptor antagonist) to assess the physiological role and importance of the α_1-adrenergic system in the regulation of circulation and metabolism, at rest and during exercise, at altitude.

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The authors wish to thank each of the volunteers who had to endure an incredibly arduous and time-consuming study.

EXECUTIVE SUMMARY

In the first two weeks of high altitude (HA) exposure, blood pressure typically rises due, in part, to a large increase in sympathetic stimulation. We hypothesized that blocking α_1-adrenergic receptors would impair circulatory compensation to an orthostatic challenge to a greater extent at HA than at sea level (SL). Sixteen healthy women (23± 2 yr) were randomly assigned to receive either 2 mg prazosin (n=8) or placebo (n=8) *t.i.d.* (double-blind design) for 12 d at SL and during the first 12 d of HA residence (4300 m). Passive 60° upright tilt was performed at SL (10 d of treatment), and after 3 and 10 d at HA. Mean arterial blood pressure (MBP, auscultation) and heart rate (HR, ECG) were measured every min during 10 min each of supine rest and tilt. *For the prazosin group compared to the placebo group*: 1. At SL, supine and tilt MBP were lower ($P<0.05$) and, at HA, MBP was lower only in the first several min of tilt on day 10 ($P<0.05$); 2. At SL or HA, HR was similar for either position; and 3. From supine to tilt, the drop in MBP was greater only at SL and the increase in HR was consistently greater only at HA (both $P<0.05$). We conclude that α_1-adrenergic blockade altered MBP and HR responses to tilt at SL and HA, but that orthostatic tolerance was well maintained in both environments. Compensatory adjustments were likely in either sympathetic and parasympathetic neural discharge or in other receptor activities.

INTRODUCTION

Well-documented ventilatory, cardiocirculatory, and hematological adjustments occur almost immediately in response to the hypoxia of altitude and continue to undergo modification for the rest of the sojourn (8,23,26,27,30-32). The level of sympathetic activity, as reflected by plasma and urinary catecholamine levels (7,17,18,29), becomes significantly elevated at rest and during exercise within 24 to 48 hours of initial altitude exposure and continues to rise over the next one to three weeks to levels that are two to three times higher than at sea level (17-19,22,29). Augmented sympathetic activity at altitude has been linked with increases in arteriolar and venous tones, blood pressure, heart rate, and adipose tissue lipolysis and with reductions in plasma volume, stroke volume, and cardiac output (4,5,10,22,23). Some of these changes --- along with other associated changes that include increases in ventilation, oxidative enzymes, myoglobin, and decreases in lactate and ammonia accumulation (15,24,27,28,29,30-32) --- at least partly compensate for the hypoxia, and gradually improve oxygen transport, exercise performance, and well being. Collectively, these findings suggested that increased sympathetic activation "orchestrated" the closely integrated and complex changes that characterize successful altitude acclimatization (18,19,22,29).

The cardiocirculatory changes in response to a rapid and passive change from the supine to upright position on a tilt table are qualitatively similar to some of the changes that occur during altitude acclimatization (5,13). With tilt, there is increased α_1-adrenergic sympathetic activity that elicits peripheral venoconstriction to minimize venous pooling and maintain venous return and stroke volume, and vasoconstriction that results in increased peripheral resistance (3-5,16,25). These responses along with cardiac acceleration via increased β-sympathetic activity (4,5,13) defend cardiac output and blood pressure during an orthostatic challenge.

We had previously considered that the cardiocirculatory demands of orthostatis would not be adequately compensated during high-altitude acclimatization. Significant altitude-induced reductions in stroke volume and cardiac output (4-6,32), and the potential of adrenergic receptor refractoriness (14) associated with continuously high blood levels of catecholamines (18,19,23) raised the possibility that additional sympathetic outflow associated with tilt would not be as effective at altitude as at sea level. Contrary to our expectations, circulatory compensation to an orthostatic challenge was well maintained during altitude acclimatization. A key finding in our studies (4-6,10) was that total peripheral resistance, reflecting augmented vasoconstriction mediated via α_1-adrenergic sympathetic activity, was consistently increased at altitude and during tilt. To determine whether increased α_1-adrenergic activity actually represents an essential response to maintain circulatory compensation during orthostatis at altitude was the purpose of the present investigation.

METHODS

SUBJECTS

Sixteen healthy women who were sea-level residents and who had normal menstrual cycles and no history of oral contraceptive use or pregnancy in the preceding year gave informed written consent to participate. Each woman underwent a medical history and a physical examination, and no one had any contraindications to altitude exposure. Prior to random assignment to a placebo (n = 8) or prazosin (n = 8) group, each subject underwent a phenylephrine challenge test (2) to determine the degree and possible adverse effects to the dose of prazosin to be used in the study. The ages, heights, and weights of the subjects in each group are presented in **Table 1.**

TABLE 1: TEST SUBJECT PHYSICAL CHARACTERISTICS		
Characteristic:	**Placebo**	**Prazosin**
Age (yr)	24 ± 6	23 ± 2
Height (cm)	164 ± 7	170 ± 9
Weight (kg)	69 ± 16	69 ± 10

Values are means ± SD

STUDY DESIGN

A double blind, placebo-controlled experimental study design was used. All testing occurred at the Geriatric Research Education and Clinical Center of the Palo Alto Veterans Administration Medical Center, Palo Alto, CA (sea level, 30 m) and while the women resided at the United States Army Pikes Peak Laboratory on the summit of Pikes Peak, CO (4300 m). A one-month interval separated the sea level and altitude phases.

Two tilt-table test sessions were conducted at sea level; a practice session and a definitive test. Two definitive tilt-table test sessions also were conducted at altitude. Total travel time by airplane and automobile from California to the summit of Pikes Peak was approximately four hours. Data from the sea level practice session were not used in any of the analyses. For all tilt-table test sessions, subjects were treated with either placebo or prazosin.

MEDICATION ADMINISTRATION

Each subject received orally either prazosin (Minipress, 2-mg *t.i.d.* or 6-mg•day^{-1}) or an identically appearing placebo at 0600, 1400, and 2200 h at sea level and altitude. At sea level, medication was administered for 14 consecutive days. Medication was also administered for an additional two days at sea level prior to traveling to Pikes Peak and then for the next 12 consecutive days while at altitude. At sea level, the definitive tilt-table test session was conducted after the subjects had been provided placebo or prazosin for 10 days; at altitude, tilt-table test

sessions were conducted on days 3 and 10 after the subjects had been provided placebo or prazosin for 5 and 12 days, respectively. Degree of α_1-adrenergic blockade was determined using a phenylephrine challenge test on day 9 at sea level and altitude. Each of the three definitive tilt-table tests was conducted approximately 3 to 4 hours after the most recent medication administration (**Table 2**).

TABLE 2: ELAPSED TIME (HOURS) BETWEEN EXERCISE TEST AND MEDICATION ADMINISTRATION

Test Day:	Placebo	Prazosin
Sea Level	3 ± 1	3 ± 1
Altitude, Day 3	4 ± 1	3 ± 1
Altitude, Day 10	3 ± 1	3 ± 1

Values are means $\pm$ SE

CATECHOLAMINE MEASUREMENTS

For a companion study (19), 24-hour urinary catecholamine samples were collected at sea level and during each day at altitude. Urinary catecholamine levels were determined by means of high-performance liquid chromatography (HPLC; model 1330 pump and model 1340 electrochemical detector, Bio-Rad) with electrochemical detection (18,19).

TILT-TABLE TEST PROCEDURES

At both locations, the same investigators used the identical tilt table, testing and calibration procedures during each of the test sessions. Ambient temperature was comfortably maintained (range: 20^0 to 23^0 C) at both locations.

Prior to each tilt-table test, electrocardiograph (ECG) electrodes were placed in the RL, V2, and V6 configuration. The subject then laid supine on a slightly padded 60-cm X 185-cm tilt-table surface. Securing straps and a footrest allowed subjects to remain passive when changing from

one position to another. A blood pressure cuff was placed around the subject's upper left arm, ECG cables were connected to the electrodes, and a small clothespin-like oximeter probe was placed on the end of the middle finger of the right hand.

For the entire duration of each tilt-table test, blood pressure, heart rate and arterial oxygen saturation were recorded continuously during quite rest for 10 to 15 min in the supine position and for 10 min in the 60° head-up position. Change in position occurred in less than 5 sec. Systemic blood pressure and heart rate were determined by noninvasive auscultation and by ECG, respectively (model 4240, Suntech, Raleigh, NC). Mean arterial blood pressure was calculated as one-third-pulse pressure plus diastolic blood pressure. Blood oxygen saturation was determined by pulse oximetry (Nellcor N-200 Pulse Oximeter, Pleasanton, CA).

DATA TABULATION AND ANALYSES

To facilitate data analyses, the supine position values for blood pressure (systolic, diastolic, and mean), heart rate, and arterial oxygen saturation at sea level and for the 3rd and 10th days at altitude are represented as a mean of minutes 4 through 9. Similarly, the upright position values for blood pressure (systolic, diastolic, and mean), heart rate, and arterial oxygen saturation are the 1st minute, and the means of minutes 4 through 6 and minutes 7 through 9.

Independent t-tests were used to determine differences between groups for age, height and weight. Two factor (group X days) analyses of variance (ANOVA) with repeated measures on one factor (days) were used to identify differences in elapsed time (hours) between exercise test and medication administrations, and blood pressure, heart rate and arterial oxygen saturation. Four-factor (group X days X position X time) ANOVA with repeated measures on three factors (days, position X time) were used to identify differences in mean arterial blood pressure, heart rate, and blood oxygen saturation between supine and upright positions. If ANOVA identified a significant

F value, Tukey's multiple comparison procedure was used to detect statistical significance of specific differences. For all analyses, a difference of $P < 0.05$ was accepted as statistically significant. Data are presented as means $\pm$ SD or as otherwise indicated.

RESULTS

PHYSICAL CHARACTERISTICS OF SUBJECTS

There were no differences ($P > 0.05$) between groups for age, height, or body weight.

ALPHA RECEPTOR BLOCKADE

At sea level and altitude, the dose of phenylephrine required to raise systolic blood pressure by 20 mmHg or more was higher ($P < 0.01$) in the prazosin group compared to the placebo group. The data in **Table 3**, collected during phenylephrine challenge tests, indicate significant α_1- adrenergic receptor blockade at sea level and altitude.

Table 3: AMOUNT OF PHENYLEPHRINE NEEDED TO INCREASE SYSTOLIC BLOOD PRESSURE BY 20 MMHG (PD_{20})

Test Day:	Placebo Group	Prazosin Group
Sea Level, Day 9	1.12 ± 0.3	6.42 ± 0.9*
Altitude, Day 9	3.91 ± 0.7	15.05 ± 2.8*

$P < 0.01$ Placebo group vs Prazosin group; PD_{20} units are $ug \cdot kg \cdot min^{-1}$; Values are means $\pm$ SE.

ELAPSED TIME

Among testing days, there were no intra- or intergroup differences in elapsed time between medication administration and the tilt-table test session that followed.

URINARY CATECHOLAMINE LEVELS

Preliminary data analyses from a companion study (19) that used the same groups of test subjects, indicated that urinary norepinephrine excretion rates increased progressively during altitude exposure and reached peak levels on days 4 and 5, and then plateaued for the remainder of

the exposure. Urinary norepinephrine levels were greater for the blocked subjects compared to the placebo subjects when measured at sea level (71% higher) and at altitude (33% higher). Urinary epinephrine excretion rates increased immediately upon altitude exposure reaching a maximum on day 3 then returned to sea level values on day 5. Epinephrine excretion rates were greater for the blocked group compared to the placebo group at sea level only (55% higher). These responses for are qualitatively similar to those previously reported for men under nearly identical environmental conditions (see ref 19).

SEA LEVEL BLOOD PRESSURE, HEART RATE AND SATURATION

Blood pressure

At sea level the blood pressures of the blocked group were lower than the blood pressures of the placebo group in both the supine and upright positions (**Table 4**) and in response to tilt (**Table 5**).

Table 4: SUPINE AND UPRIGHT BLOOD PRESSURES AT SEA LEVEL

Group:	Supine	Min 1	Mins 4 to 6	Mins 7 to 9
Systolic BP				
Placebo	111 ± 9	115 ± 10	115 ± 8	116 ± 8
Blocked	107 ± 6	104 ± 10*	103 ± 7*	103 ± 6*
Diastolic BP				
Placebo	68 ± 7	76 ± 4[a]	73 ± 7	74 ± 7
Blocked	62 ± 4*	64 ± 6*	64 ± 5*	68 ± 14
Mean BP				
Placebo	82 ± 7	89 ± 6[##]	87 ± 5	88 ± 7
Blocked	77 ± 4*	78 ± 6*	77 ± 5*	79 ± 10

Values are in units of mmHg and are means ± SD; ; n = 8 for each group;
*P < 0.05, differs from placebo; [##]P < 0.05, differs from supine position; [a]P = 0.076, from supine position

Table 5: BLOOD PRESSURE RESPONSES TO TILT AT SEA LEVEL			
Group:	**Min 1**	**Mins 4 to 6**	**Mins 7 to 9**
Systolic BP			
Placebo	3 ± 5	3 ± 5	4 ± 6
Blocked	-3 ± 6*	-4 ± 4*	-4 ± 2*
Diastolic BP			
Placebo	8 ± 4	6 ± 4	6 ± 5
Blocked	2 ± 6*	2 ± 4*	6 ± 13
Mean BP			
Placebo	7 ± 3	5 ± 3	5 ± 4
Blocked	1 ± 5*	0 ± 3*	3 ± 8

[+]Response is calculated as ([tilt time] minus supine); n = 8 for each group
Values are in units of mmHg and are means ± SD; *P < 0.05, differs from placebo.

Heart Rate and Arterial Oxygen Saturation

Heart rates did not differ between groups for either position. For both groups, heart rate in the upright position was greater than heart rate in the supine position and remained higher with continued time of tilt (P < 0.05). Arterial saturations did not differ between groups in both positions and did not change from supine to upright tilt (**Table 6**). In response to tilt, the change in heart rate was similar for both groups except for a greater heart rate response of the blocked group during minutes 7 to 9 (**Table 7**).

Table 6: SUPINE AND UPRIGHT HEART RATE AND SATURATION AT SEA LEVEL				
Group:	**Supine**	**Min 1**	**Mins 4 to 6**	**Mins 7 to 9**
Heart Rate				
Placebo	59 ± 8	74 ± 15[##]	74 ± 15[##]	74 ± 13[##]
Blocked	57 ± 10	78 ± 14[##]	78 ± 14[##]	84 ± 18[##]
Saturation				
Placebo	97 ± 0	97 ± 0	97 ± 0	97 ± 0
Blocked	97 ± 0	97 ± 0	97 ± 0	97 ± 0

Heart rate units are beats per min and saturation units are percentages; Values are means ± SD; n = 8 for each group; *P < 0.05, differs from placebo; [##]P < 0.05, differs from supine position

Table 7: HEART RATE AND SATURATION RESPONSES TO TILT AT SEA LEVEL			
Group:	Min 1	Mins 4 to 6	Mins 7 to 9
Heart Rate			
Placebo	15 ± 8	14 ± 7	15 ± 7
Blocked	21 ± 6	22 ± 7	27 ± 14*
Saturation			
Placebo	0 ± 0	0 ± 0	0 ± 0
Blocked	0 ± 0	0 ± 0	0 ± 0

[+]Response is calculated as ([tilt time] minus supine); n = 8 for each group
Heart rate units are beats per min and saturation units are percentages; Values are means ± SD; *P < 0.05, differs from placebo.

ALTITUDE, DAY 3; BLOOD PRESSURE, HEART RATE AND SATURATION

Blood Pressure

For the blocked group compared to the placebo group, the supine or upright blood pressures did not differ (**Table 8**; $P > 0.05$) and the blood pressure response to tilt did not differ (**Table 9**; $P > 0.05$). However, blood pressure variability --- as reflected in the greater standard deviation values in both tables --- increased noticeably from sea level. Diastolic and mean blood pressures increased more on the third day at altitude compared to sea level, respectively, in the supine position and during the first min of tilt in the blocked group ($P < 0.05$). Supine or upright blood pressures for the placebo group were not increased on the third day at altitude compared to sea level ($P < 0.05$; **Table 8**).

Table 8: SUPINE AND UPRIGHT BLOOD PRESSURES AT ALTITUDE, DAY 3				
Group:	Supine	Min 1	Mins 4 to 6	Mins 7 to 9
Systolic BP				
Placebo	117 ± 8	119 ± 18	117 ± 13	116 ± 14
Blocked	110 ± 8	106 ± 11	108 ± 10	108 ± 10
Diastolic BP				
Placebo	72 ± 9	73 ± 10	76 ± 11	75 ± 8
Blocked	68 ± 6#	73 ± 10#	71 ± 10	74 ± 11
Mean BP				
Placebo	87 ± 7	88 ± 11	89 ± 10	89 ± 9
Blocked	82 ± 6#	84 ± 10#	84 ± 10	85 ± 10

Values are in units of mmHg and are means ± SD; n = 8 for each group

*P < 0.05, differs from placebo; #P < 0.05, differs from sea level

Table 9: BLOOD PRESSURE RESPONSES TO TILT AT ALTITUDE, DAY 3			
Group:	**Min 1**	**Mins 4 to 6**	**Mins 7 to 9**
Systolic BP			
Placebo	2 ± 12	0 ± 8	-1 ± 8
Blocked	-4 ± 11	-2 ± 7	-2 ± 7
Diastolic BP			
Placebo	1 ± 7	4 ± 6	3 ± 8
Blocked	5 ± 7	4 ± 6	6 ± 7
Mean BP			
Placebo	1 ± 7	2 ± 6	1 ± 7
Blocked	2 ± 8	2 ± 6	3 ± 6

+Response is calculated as ([tilt time] minus supine); n = 8 for each group

Values are in units of mmHg and are means ± SD

Heart Rate and Arterial Oxygen Saturation

Heart rate did not differ between groups for either position with the exception of a higher value for the blocked group in the first min of tilt (P < 0.05). For both groups, heart rate in the upright position was greater than heart rate in the supine position and remained significantly

higher from supine with continued time of tilt ($P < 0.05$). For both positions, heart rates were higher on day 3 at altitude than at sea level, respectively ($P < 0.05$). Arterial saturation did not differ between groups for both positions; but values were lower for both groups on day 3 at altitude than at sea level ($P < 0.05$). During the first minute of tilt, saturation increased from supine for both groups ($P < 0.05$) before returning towards supine values (**Table 10**). In response to tilt, the supine to tilt changes in heart rate were greater for the blocked group than for the placebo group throughout the tilt period ($P < 0.05$); but no between group differences existed for saturation (**Table 11**).

Table 10: SUPINE AND UPRIGHT HEART RATE AND SATURATION AT ALTITUDE, DAY 3

Group:	Supine	Min 1	Mins 4 to 6	Mins 7 to 9
Heart Rate				
Placebo	$84 \pm 13^{\#}$	$95 \pm 16^{\#,\#\#}$	$102 \pm 12^{\#,\#\#}$	$102 \pm 13^{\#,\#\#}$
Blocked	$79 \pm 11^{\#}$	$104 \pm 10^{*,\#,\#\#}$	$104 \pm 10^{\#,\#\#}$	$104 \pm 9^{\#\#}$
Saturation				
Placebo	$82 \pm 4^{\#}$	$89 \pm 4^{\#,\#\#}$	$85 \pm 3^{\#}$	$86 \pm 4^{\#}$
Blocked	$85 \pm 5^{\#}$	$89 \pm 3^{\#,\#\#}$	$88 \pm 4^{\#}$	$87 \pm 3^{\#}$

Heart rate units are beats per min and saturation units are percentages; Values are means ± SD; n = 8 for each group; *P < 0.05, differs from placebo; #P <0.05, differs from sea level; ##P < 0.05, differs from supine position

Table 11: HEART RATE AND SATURATION RESPONSES TO TILT AT ALTITUDE, DAY 3

Group:	Min 1	Mins 4 to 6	Mins 7 to 9
Heart Rate			
Placebo	11 ± 11	17 ± 8	18 ± 8
Blocked	$25 \pm 10^{*}$	$24 \pm 11^{*}$	$25 \pm 8^{*}$
Saturation			
Placebo	6 ± 6	3 ± 4	4 ± 4
Blocked	4 ± 3	3 ± 3	2 ± 2

+Response is calculated as ([tilt time] minus supine); n = 8 for each group

Heart rate units are beats per min and saturation units are percentages; Values are means ± SD; *P < 0.05, differs from placebo.

ALTITUDE, DAY 10; BLOOD PRESSURE, HEART RATE AND SATURATION

Blood Pressure

Supine blood pressure did not differ between groups. During tilt, diastolic and mean blood pressures of the blocked group were lower than those of the placebo group through the first six mins of tilt. After the 6th min of tilt, two subjects in the blocked group requested that they be returned to the supine position (**Table 12**). In both cases, the subjects complained of lightheadedness. Diastolic and mean blood pressures for the blocked group --- but not the placebo group --- were greater on day 10 at altitude than at sea level ($P < 0.05$). There were no blood pressure differences between groups in response to tilt ($P > 0.05$, **Table 13**).

Table 12: SUPINE AND UPRIGHT BLOOD PRESSURES AT ALTITUDE, DAY 10

Group:	Supine	Min 1	Mins 4 to 6	Mins 7 to 9
Systolic BP				
Placebo	112 ± 8	111 ± 10	112 ± 14	107 ± 10
Blocked	111 ± 9	113 ± 20	100 ± 17	103 ± 17
Diastolic BP				
Placebo	71 ± 4	77 ± 8	73 ± 7	70 ± 7
Blocked	68 ± 4#	64 ± 10*	64 ± 7*	65 ± 7
Mean BP				
Placebo	85 ± 4	88 ± 7	86 ± 9	83 ± 7
Blocked	82 ± 5#	80 ± 6*	76 ± 10*	78 ± 9

Values are in units of mmHg and are means ± SD; n = 8 for each group except (n = 6) for mins 7 to 9 for the blocked group; *P < 0.05, differs from placebo; #P <0.05, differs from sea level

Table 13: BLOOD PRESSURE RESPONSES TO TILT AT ALTITUDE, DAY 10			
Group:	Min 1	Mins 4 to 6	Mins 7 to 9
Systolic BP			
Placebo	-1 ± 16	-1 ± 19	-5 ± 16
Blocked	2 ± 25	-11 ± 13	-10 ± 12
Diastolic BP			
Placebo	6 ± 10	1 ± 7	-1 ± 6
Blocked	-4 ± 8	-3 ± 7	-3 ± 9
Mean BP			
Placebo	3 ± 9	1 ± 10	-2 ± 8
Blocked	-2 ± 6	-6 ± 8	-5 ± 9

[+]Response is calculated as ([tilt time] minus supine); n = 8 for each group except (n = 6) for mins 7 to 9 for the blocked group; Values are in units of mmHg and are means ± SD; *P < 0.05, differs from placebo.

Heart Rate and Arterial Oxygen Saturation

Heart rate did not differ between groups for either position (P > 0.05). For both groups, heart rate in the upright position was greater than heart rate in the supine position and remained significantly higher from supine with continued time of tilt (P < 0.05). For both positions, heart rates were higher on day 3 at altitude than at sea level, respectively (P < 0.05). Arterial saturation did not differ between groups for both positions; but values were lower for both groups on day 3 at altitude than at sea level (P < 0.05; **Table 14**). In response to tilt, the supine to tilt changes in heart rate were greater for the blocked group than for the placebo group throughout the tilt period (P < 0.05); but no between group differences existed for saturation (**Table 15**).

Table 14: SUPINE AND UPRIGHT HEART RATE AND SATURATION AT ALTITUDE, DAY 10				
Group:	**Supine**	**Min 1**	**Mins 4 to 6**	**Mins 7 to 9**
Heart Rate				
Placebo	$75 \pm 15^{\#}$	$100 \pm 16^{\#,\#\#}$	$101 \pm 17^{\#,\#\#}$	$103 \pm 19^{\#,\#\#}$
Blocked	$72 \pm 13^{\#}$	$103 \pm 12^{\#,\#\#}$	$107 \pm 10^{\#,\#\#}$	$107 \pm 13^{\#,\#\#}$
Saturation				
Placebo	$90 \pm 4^{\#}$	$92 \pm 2^{\#}$	$90 \pm 3^{\#}$	$91 \pm 3^{\#}$
Blocked	$89 \pm 2^{\#}$	$92 \pm 1^{\#}$	$91 \pm 2^{\#}$	$90 \pm 2^{\#}$

Heart rate units are beats per min and saturation units are percentages; Values are means ± SD; n = 8 for each group except for minutes 7 to 9 for the blocked group (n = 6); *P < 0.05, differs from placebo; #P <0.05, differs from sea level; ##P < 0.05, differs from supine position

Table 15: HEART RATE AND SATURATION RESPONSES TO TILT AT ALTITUDE, DAY 10			
Group:	**Min 1**	**Mins 4 to 6**	**Mins 7 to 9**
Heart Rate			
Placebo	25 ± 11	26 ± 11	28 ± 12
Blocked	32 ± 12*	35 ± 13*	35 ± 17*
Saturation			
Placebo	2 ± 2	0 ± 3	1 ± 3
Blocked	3 ± 2	2 ± 3	0 ± 2

+Response is calculated as ([tilt time] minus supine); n = 8 for each group except for minutes 7 to 9 for the blocked group (n = 6); Heart rate units are beats per min and saturation units are percentages; Values are means ± SD; *P < 0.05, differs from placebo.

DISCUSSION

Previous clinical use of prazosin at sea level indicated that it inhibited vasoconstriction induced by endogenous catecholamines and caused vasodilatation in both arteriolar resistance vessels and veins (9,12). Moreover, the magnitude of the resulting fall in blood pressure was directly proportional to the levels of sympathetic nerve activity and hypohydration at the time of drug administration (9,11,20). The implication for the present study was that since large increases were expected at altitude in sympathetic activity and fluid loss (5,10,17,18,23), α_1-adrenergic receptor blockade would impair blood pressure compensation to an orthostatic challenge more at altitude than at sea level. However, the results of the present study indicate that supine and tilt blood pressures were affected by α_1-adrenergic receptor blockade more at sea level than at altitude and that orthostatic tolerance was generally well maintained in both environments.

One possible explanation for this finding was that significant α_1-adrenergic blockade was not present during the all tilt tests due either to an insufficient dose of prazosin to cause blockade or to a time delay between drug dosing and tilt testing that was too long to assure adequate blockade. This possibility is not tenable. The amount of phenylephrine needed to raise systolic blood pressure 20 mmHg in the blocked group compared to the placebo group was on average nearly six times higher at sea level and nearly four times higher at altitude. Also, tilt-table tests were conducted in both environments an average of about three hours after drug administration, a period of time that was well within the four to six hour duration of action (1,11,20). It is also likely that the tilt tests were performed when the plasma concentrations were highest and there was a high degree of α_1-adrenergic receptor blockade since time to peak concentration of prazosin occurs one to three hours after ingestion (1,11). Taken together, these data clearly support the notion that significant α_1-adrenergic receptor blockade was present during the conduct of all tilt

tests.

A companion study reported that urinary noreprinephrine excretion rates were greatly increased at altitude compared to sea level for both groups; but were much higher for the blocked group compared to the placebo group at sea level and altitude. Urinary epinephrine levels also were much higher for both groups during the first few days of altitude compared to sea level and were higher for the blocked group than for the placebo group; but only at sea level. Moreover, the amount of phenylephrine needed to raise blood pressure by 20 mmHg was two to four times greater for both groups at altitude than at sea level. This last result suggests that α_1-adrenergic receptors were becoming relatively refractory to the sustained altitude-induced increased level of sympathetic activity. Thus, another, and more probable explanation for the apparently adequate blood pressure compensation to an orthostatic challenge despite α_1-adrenergic blockade, likely involved compensatory adjustments in sympathetic and parasympathetic neural discharge, and/or receptor activity modification that enhanced the importance of other means of circulatory compensation (4,12,14).

At sea level, as expected, blood pressure for both positions was lower for the blocked group than for the placebo group. In response to tilt, blood pressure for the placebo group tended to increase; but for the blocked group there was little change. In contrast, supine and tilt heart rates, and the response of heart rate to tilt, were similar between groups. The similarity in heart rates occurred despite a large difference between groups in sympathetic activation as evidenced by a 71% higher urinary norepinephrine levels and 55% urinary epinephrine values for the blocked group compared to the placebo group (19). Nevertheless, our blood pressure and heart rate results are consistent with clinical observations at sea level showing that the actions of prazosin are confined mainly to the resistance vessels, and that there is little reflex tachycardia (9,21).

A somewhat different picture emerges during altitude exposure, however. On day three there were no between group differences for blood pressure for either position or for the blood pressure response to tilt. Interestingly, despite similar α_1-adrenergic receptor blockade at sea level and at altitude for the blocked group, the blood pressure values on day three were consistently higher than the blood pressure values at sea level. On day 10, supine and tilt blood pressures of the blocked group tended to be lower than those of the placebo group, and were also lower compared to day 3. In contrast, blood pressures were much more stable from the 3rd to the 10th day at altitude for the placebo group. For both altitude test days, the heart rate response to tilt was consistently greater for the blocked group than for the placebo group. Since blood pressure is the product of total peripheral resistance, heart rate and stroke volume, it is likely that the greater response of heart rate to tilt for the blocked group was sufficient to adequately compensate for the decline in total peripheral resistance and fluid loss (26, 32) at altitude. (Altitude-induced fluid loss was similar for each group (unpublished data)).

Tachycardia associated with tilt is a combination of an increase in sympathetic tone and a reduction in parasympathetic tone (13,25). Thus the greater compensatory increase in heart rate for the blocked group during tilt could reflect either greater levels of either cardiac β-sympathetic stimulation or parasympathetic inhibition. In the present study, the higher heart rate in the blocked group is likely to have resulted more from parasympathetic withdrawal than from cardiac β-adrenergic stimulation. Persistently high blood catecholamines levels associated with altitude exposure have been linked with reduced cardiac β-adrenergic responsiveness (14). Moreover, since the blocked group had much higher sustained blood catecholamine levels, it is probable that they experienced a greater degree of cardiac β-receptor refractoriness, and thus greater parasympathetic withdrawal, than the placebo group. That parasympathetic withdrawal can

contribute successfully as a compensatory response to the tachycardia associated with passive tilt at altitude more so than at sea level was previously reported by our group (4). In that study, despite total β-adrenergic receptor blockade at sea level and altitude, heart rate increased by ~25 beats per min during tilt at altitude but by only 17 beats per min at sea level.

Supine and tilt arterial oxygen saturations did not differ between groups at sea level or altitude. With altitude exposure, supine arterial oxygen saturation was reduced from sea level for both groups approximately by 16% on day 3 and by 10% on day 10. The initial large decrement and subsequent improvement in saturation at altitude is a well-documented response characterizing successful altitude acclimatization (8,32). The slightly higher value observed in the tilt position relative to the supine position (especially in the first minute) at altitude is due to a position-related hyperventilation that is also a well documented response (13).

SUMMARY

During altitude acclimatization or in response to upright tilt, there is heightened sympathetic stimulation that has been linked to increases in blood and urinary levels of catecholamines, blood pressure, arteriolar constriction, and heart rate. Previous studies indicated that circulatory compensation to a passive orthostatic challenge was well maintained during altitude acclimatization despite significant reductions in plasma volume and stroke volume. A key finding in these studies was that total peripheral resistance, reflecting augmented vasoconstriction mediated via α_1-adrenergic sympathetic activity, was consistently increased at altitude and during tilt. In the present study we tested the postulate that increased α_1-adrenergic sympathetic activity was an essential response to maintain circulatory compensation during an orthostatic challenge at altitude. Our approach was to administer prazosin, a selective α_1-adrenergic receptor antagonist, to healthy women during altitude acclimatization and measure their responses to tilt. A high

degree of α_1-adrenergic receptor blockade at sea level and altitude was confirmed by pharmacological challenge and a large increase in sympathetic discharge was confirmed by high levels of urinary catecholamines. At sea level, prazosin reduced supine and tilt blood pressures; at altitude, it had no effect on day 3, and a moderate effect on day 10. At altitude, blood pressure during tilt was apparently sufficiently maintained by a compensatory increase in heart rate, likely mediated by parasympathetic withdrawal.

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